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TRANSACTIONS

OF

The Society of Tropical Medicine and Hygiene.

THE PARASITE OF KALA-AZAR AND ALLIED ORGANISMS.

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(*Friday, January* 15, 1909.)

Shortly after my return to England I was asked to read a paper on "Kala-Azar" before this Society, and on considering what particular aspect of the disease I was most competent to deal with, I decided to limit myself to the parasite, so to-night I propose to give you some account of my observations on this organism and its allies. I have no doubt you are all well acquainted with the parasite, the discovery of which has opened up an entirely new field of research of great practical importance. Although we now know a great deal about it and its two allies, the parasites of infantile splenomegaly and Oriental sore, there is considerable doubt as to their exact systematic position. Laveran and Mesnil, I believe, still regard the parasite of kala-azar as belonging to the genus *Piroplasma*, while you will remember Ross placed it as an entirely new genus, *Leishmania*. The view

that this parasite is a hæmocytozoon can no longer be entertained, and Christophers' recent studies on the extracorporeal life-cycle of *Piroplasma canis* in the tick have shown that it does not pass through a flagellate stage similar to that of the parasite of kala-azar. I am aware that certain observers claim to have discovered flagellate stages in some Piroplasmata; their observations, however, are far from convincing. I have recently seen some of these so-called piroplasma flagellates, and have no hesitation in saying that they do not bear any resemblance to the characteristic flagellates of the parasite of kala-azar. It should also be noted that these flagellate stages of Piroplasmata have so far only been seen in test-tubes or in the blood of the vertebrate host, whereas they ought to occur naturally in ticks or other invertebrates.

There is, however, no doubt that the parasite of kala-azar and its two allies, as seen in man, are but stages in the life-histories of flagellates, and the important question to answer is, do they belong to any known group of the parasitic flagellata? As our knowledge of the life-cycles of these organisms is exceedingly limited, I think it somewhat premature to say they belong to an entirely new genus, and I hope to show you that they do belong to a group which has long been recognized as occurring in the alimentary tracts of insects. From a study of the flagellates of the parasite of kala-azar in the test-tube, as well as in the bed-bug *Cimex rotundatus*, I have no hesitation in saying it is not a trypanosome; for, like all other observers who have studied this stage, I have never seen anything similar to the well-known vertebrate trypanosome.

The most important suggestion as to the nature of the parasite of kala-azar was undoubtedly made by

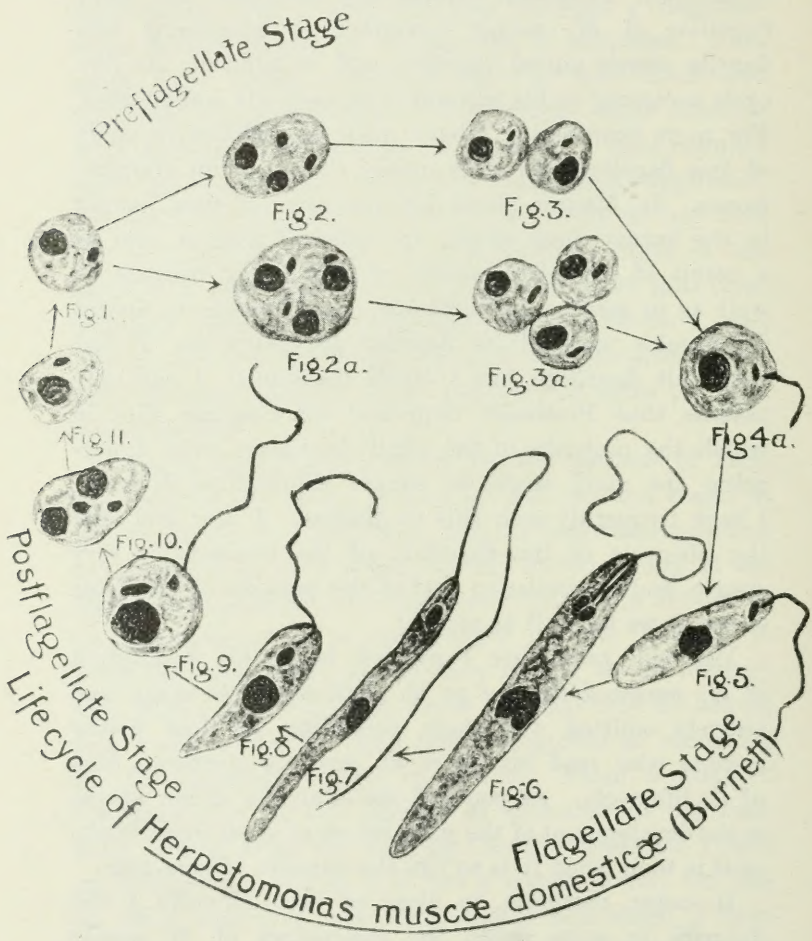
Rogers, who, on comparing it with *Herpetomonas muscæ domesticæ*, as figured by Prowazek, recognized the close similarity in the build of the two flagellates. Unfortunately, Prowazek erroneously described the adult flagellate of *H. muscæ domesticæ* as possessing two flagella closely united together, and, in addition, its life-cycle according to his account is exceedingly complicated. For more than a year I have made an exhaustive study of this flagellate, the type species of the genus *Herpetomonas*. In Madras about 100 per cent. of flies, caught in the bazaar meat shops, are infected with it, and as a result of my observations on the living parasite as well as in stained preparations, I am unable to accept Prowazek's view of its flagellar apparatus, for I find the adult flagellate has a single flagellum. I can only assume that Prowazek happened to examine flies in which the majority of the adult flagellates were undergoing the early stages of simple longitudinal division; I have frequently seen this in Madras. I also find that the life-cycle of the flagellate of the house-fly is very simple, and is similar to that of the parasite of kala-azar so far as we know it at present.

You will remember Prowazek began his description of *H. muscæ domesticæ* at its adult flagellate stage, and entirely omitted the stage preceding it, thus giving anyone who read his paper an entirely erroneous idea of its life-cycle. As you will see later, the earlier stages in the development of the parasite are of great importance, as it is then when it is so like the parasite of kala-azar.

In order, therefore, to clear up this difficulty I will describe in some detail the life-history of *H. muscæ domesticæ*, the complete account of which I shall reserve for another occasion. After having studied a large number of these parasites I have found it convenient

to divide their life-cycles into three stages, *preflagellate*, *flagellate* and *postflagellate*, and it should be clearly

PLATE I.



understood there is no hard and fast line dividing one stage from the other; they merge into each other. You will, however, see that by studying these flagellates

along these lines it is easy to work out their complete life-histories, and, above all, to find out how they pass from one host to another. In the case of *H. muscæ domesticæ* in Madras the *flagellate* and *postflagellate* stages are readily found, but owing to the fact that a large number of flies have to be examined before the *preflagellate* stages can be studied, this important portion of the life-cycle of the parasite is very apt to be missed.

The *preflagellate* (Plate I., figs. 1 to 3*a*) stage is usually found in the midgut, the parasites lying in masses within the peritricheal membrane; they are round or slightly oval bodies, measuring on an average about 5·5 μ in breadth, and contain a nucleus, a blepharoplast, and a number of granules. They multiply by simple longitudinal fission or by multiple segmentation (figs. 2, 2*a*, 3, 3*a*), so that very soon a large number of these bodies is formed. The *flagellate* stage is characterized by the formation of the flagellum, a single stout filament which projects freely from a point in close proximity to the blepharoplast (fig. 4); the resulting flagellates elongate and later divide by simple longitudinal division (figs. 5, 6 and 7). The nucleus of the adult flagellate lies about the centre, and the blepharoplast, a large rod-shaped body, is nearly always situated a short distance from the anterior end; the flagellum is a single filament which projects freely almost at once from the rounded anterior end. The early stage of the process of longitudinal fission begins by a splitting of the root of the flagellum, and this, as well as further stages of the same change, led Prowazek to believe *H. muscæ domesticæ* has a double flagellum. Had he, however, studied the method of formation of the flagellum he would not have fallen into this error. It is quite a common thing to find nearly all the adult flagellates in a fly exhibiting

this appearance of a double flagellum. If the mid-guts of a number of flies are next examined in the fresh condition, in some, the flagellates will be seen collecting together towards the rectum, they attach themselves in rows by their flagellar ends to the gut-wall, and now further changes are seen to occur. The most external parasites begin to shorten, and while this change is taking place the flagellum degenerates and is eventually shed (figs. 8 and 9). A palisade of parasites is now formed, the most internal showing the changes noted above, while the most external are seen as round bodies devoid of flagella, and many of these latter forms are seen dividing again (fig. 10). Eventually, all the bodies round up and are connected together by a sticky substance, and these masses of cells constitute the cysts (fig. 11); this I regard as the *postflagellate* stage. These cysts are passed out in the fæces of the fly *en masse* and are well adapted to resist desiccation. It is these bodies which are again sucked up accidentally by the flies as they feed. Such is a short account of the life-cycle of *H. muscæ domesticæ;* it is exceedingly simple, for I can find no evidence of the complicated sexual changes described by Prowazek.

Turning now to another herpetomonad, *H. lygæi*, which I have recently described, you will see that it has a very similar life-cycle, only in this case the parasite is almost identical with that of kala-azar. In its *preflagellate* stage it is a small round or pear-shaped body (Plate II., fig. 1), measuring from 3·5 μ to 4 μ in length; it has a nucleus and blepharoplast and is found lying free in the mid-gut of *Lygæus militaris*. The parasite divides, by simple fission into two, and each half again divides, so that four oval bodies are formed (figs. 2, 3 and 4). These bodies now pass on to flagellation somewhat

irregularly (figs. 5, 6 and 7), so that one may have developed into an adult flagellate while the remainder are dividing further and remain attached to its anterior end (fig. 7). The adult flagellates divide by simple longitudinal division (figs. 8 and 9), and eventually collect in the hind-gut of the bug, where they attach themselves in rows; they now shorten (fig. 10), the flagella degenerate (fig. 11) and are shed, and they divide (fig. 12) at least twice (fig. 13), resulting in small pear-shaped bodies, the cysts, which are passed out in the fæces of the bug (fig. 14).

I have already described in great detail the development of the parasite of kala-azar in twelve bed-bugs (*Cimex rotundatus*), and if you refer to my illustrations you will find its life-cycle, so far as it is known, is very similar to that of the two herpetomonads I have just described. All three parasites are very similar in their preflagellate stages, except that *H. muscæ domesticæ* is much larger; they develop and multiply in the same way, and in their adult flagellate stage they have the same general morphological build. They all undergo their developmental stages in the intestinal tracts of insects, but the fact that one of them passes its *preflagellate* stage in man has led most observers to regard it as something quite distinct from a *Herpetomonas*. The parasite of kala-azar is certainly not a sporozoon; it remains throughout its life-cycle, as far as we know it, a typical flagellate. With a complete knowledge of the life-cycle of such a closely allied form as *H. lygæi* it is possible to conjecture that the parasite of kala-azar, in order to get back to man, must pass back again to a non-flagellate stage, *postflagellate*, and that this change is most likely to take place somewhere in the neighbourhood of the biting parts of the bed-bug. Had I known the

complete life-cycle of *H. lygæi* when I had my heavily-infected bugs I might have been able to solve this problem. This emphasizes the importance of studying these seemingly unimportant parasites, and I am sorry to say there are some people who still think it is a waste of time to study such forms, but there is no doubt that a knowledge of their life-cycles is of the utmost importance in helping to explain those of more complex pathogenic protozoa.

I have now shown you that the parasite of kala-azar is a *Herpetomonad*, and that in its *preflagellate* stage it may be indistinguishable from a harmless species; this truth is of importance, because in spite of other data the two closely allied human forms—the parasites of infantile splenomegaly and Oriental sore—are still regarded as identical with the parasite of kala-azar. I know at least three closely allied *Herpetomonads* which are very similar in their preflagellate stages to *H. muscæ domesticæ* so that this similarity in one stage is of little importance in distinguishing between these species. The parasite of kala-azar should, therefore, be known as *H. donovani* (Laveran and Mesnil), the parasite of infantile splenomegaly as *H. infantum* (Nicolle), and the parasite of Oriental sore as *H. tropica* (Wright), and I would suggest the diseases produced by these parasites should be collectively known as Herpetomoniases.

It is most unfortunate that all attempts to transmit *H. donovani* to animals have entirely failed; quite recently I inoculated dogs with the parasite, with negative results. It seems to me, therefore, that it will be well-nigh impossible to prove finally that *C. rotundatus* is the carrier of this dangerous parasite. It is to be hoped, therefore, that exhaustive feeding experiments, similar to those I carried out in Madras, will be conducted with

H. infantum and *H. tropica*. However, I feel bound to say here that there is too great a tendency at present to cultivate these parasites in test-tubes ; these experiments are undoubtedly highly interesting, yet they will not give us the clue as to how the parasites are transmitted from man to man. Feeding experiments with blood-sucking insects in the case of these *Herpetomonads* are very difficult and tedious, owing to the fact that unless a very good case is selected it is almost impossible to follow one or two developing parasites in the guts of blood-sucking insects. Further, such experiments must be carried out with great precision, and the observer must possess a good working knowledge of the many harmless gut flagellates which occur in nearly every insect. So far as I am aware, no attempts have been made to discover the transmitting agent of *H. infantum* or *H. tropica*.

Discussion.

Dr. Sambon said that he wished to express his very high appreciation of Captain Patton's work on kala-azar. Captain Patton had pointed out that the cell-enclosed "Leishman-Donovan bodies" became numerous in the peripheral blood of kala-azar patients in the later stages of the disease, and he had shown by feeding experiments that in the mid-gut of the rounded bed-bug (*Cimex rotundatus*) they assumed the flagellate form obtained by Major Leonard Rogers in artificial culture media. Furthermore, he had endeavoured to work out the entire life-history of the parasite, not only by following its development in the bed-bug, but also by studying allied organisms in other insects.

The slow rate of the bed-bug's dispersion and the

strictly domestic habits of this blood-sucking pest, were in perfect accordance with the peculiar epidemiology of the disease, and, no doubt, the destruction of bed-bugs might prove a very important, if not the most essential element, in the prevention of kala-azar.

With Captain Patton, he believed that a double flagellum, in some of the free active forms of the kala-azar parasite and closely allied organisms, was merely evidence of incipient binary fission. However, other organisms had been described which certainly possessed two flagella. In the corresponding culture-forms of the trypanoplasmata, they would naturally expect to find two flagella arising from the anterior end of the single, undividing individuals, and two pairs of flagella in the dividing forms.

No doubt, it would soon be necessary to break up the trypanosominæ into a greater number of genera than he (Dr. Sambon) had done in his classification of the Hæmoprotozoa, but, for the time being, owing to the very imperfect state of their knowledge on the complicated life-history of these parasites, he was unable to adopt the genera *Crithidia* and *Herpetomonas*, proposed by Léger some years ago when still less was known. The forms thus named appeared to him to represent only particular stages in the life-history of organisms they would certainly ascribe either to the genus *Trypanoplasma* or to the genus *Trypanosoma*, did they know the relative free forms in the blood of the respective vertebrate hosts. Indeed, it was more than likely that, in many cases, both the trypanosoma- and herpetomonas-forms of a same organism were known, but that their relationship had escaped them. It was a well-known fact that many trypanosomes, of which they had been able to obtain culture-forms, exhibited, in the artificial

medium, a herpetomonas-form similar to that which they would no doubt assume within the gut of the necessary invertebrate host. Small circular, oval or pear-shaped forms, with two nuclear masses and no locomotor apparatus, were found both in the tissues of the vertebrate host alongside with the trypanosoma-forms, and in the stomach of the invertebrate host with the herpetomonas-forms. They represented a resting intermediary stage between the two forms. Similar bodies had been described not only in cases of kala-azar and Oriental sore, but also, by several investigators, in various animal trypanosomiases. Described first by Bradford and Plimmer in nagana, and by Castellani in human trypanosomiasis, they had been seen by himself unmistakably in the cerebrospinal fluid and tissues of sleeping-sickness patients and nagana-infected animals.

He considered the life-cycles of the kala-azar parasite, of *Herpetomonas lygæi* and *Crithidia gerridis*, as sketched out by Captain Patton, to be quite incomplete. Indeed, the forms described by the lecturer were but the very first stages which could be seen equally well in artificial cultures. Evidently, Captain Patton had missed the conjugation forms, and the resulting oökinetes, and all the subsequent stages which led to the forms destined to be inoculated into a fresh vertebrate host. The forms the lecturer termed "encysted" he could not accept as such; there was no evidence whatever of encystment in either the figures or descriptions he had published. His "postflagellate" forms were identical with those he called "preflagellate," and which no doubt represented the forms taken up directly from the vertebrate host. The fact that they might occur in the fæces was no evidence; Captain Patton had not found round and oval forms alone in the fæces, but also the long, flagellate

forms which, obviously, could not be looked upon as encysted. The oval forms were, no doubt, transition forms between the round and long flagellate forms. The round forms did not present the characteristic capsule of encysted forms.

Dr. Sambon maintained that the most important stages in the sporogony of the Trypanosominæ had so far escaped the observation, not only of Captain Patton, but of most investigators, notwithstanding that in closely allied groups Schaudinn had traced them in a masterly way. However, certain stages had been observed separately in one or other species. Thus, a number of investigators—such as Prowazek, Lühe, Minchin, &c.—had described a marked trimorphism in several species. He (Dr. Sambon) had seen it himself most evidently in *Trypanosoma gambiense*. Indeed, he had been the first to describe differentiated sporonts in *T. gambiense*, not from the gut of the fly, but from the peripheral blood of man. Conjugation forms had been seen by Prowazek in *T. lewisi* within the mid-gut of the rat-louse (*Hæmatopinus spinulosus*), and the same interpretation might be given, he believed, to the kala-azar parasites described by Major Leishman, as "splitting off a thin spirillum-like form by unequal longitudinal division."

The oökinete after encystment—true encystment indicated in stained specimens by the numerous pink granules which beset the capsule—had been described by Prowazek in *Herpetomonas muscæ*, by Minchin in *Trypanosoma grayi*, and by Flu in *Crithidia melophagia*. Both Prowazek and Flu had found these encysted forms in the ovaries of the very different flies they had examined, and thus indicated the great probability of hereditary transmission for the respective parasites. This mode of transmission he (Dr. Sambon) had indicated as early

as June, 1903, for *Trypanosoma gambiense*, basing his suggestion on a number of facts, analogies and arguments, which must inevitably prove correct. Already his suggestion had received considerable support from the observations of Schaudinn, Prowazek, Minchin and Flu, and, when properly interpreted, from the numerous experiments carried out by Sir David Bruce and others, to prove the transmission of sleeping sickness and certain animal trypanosomiases by tsetse-flies. Of course he (Dr. Sambon) was quite prepared to find a modified life-cycle in the forms which inhabited non-phlebotomous insects; but so far as the parasites of sleeping sickness and kala-azar were concerned, if they wished to understand their life-histories, they should compare them with those of similar organisms found in blood-sucking insects. However, many facts in the natural history of kala-azar led him to think that the organism which gave rise to that disease might provide for its dispersion in various ways, availing itself both of blood-sucking and non-phlebotomous insects.

There was another important question on which his opinion differed from that of Captain Patton, and that was the question of relationship between the various morbid manifestations in which "Leishman-Donovan bodies" had been found.

When Wright described, in a case of Oriental sore, parasites indistinguishable from those discovered by Major Leishman in kala-azar, Sir Patrick Manson suggested the possible identity of the parasites found in the two diseases. In the fourth edition of his book on "Tropical Diseases," he said: "If the parasite of Oriental sore be specifically identical with that of kala-azar, it must somehow have been deprived of its virulence; for, although kala-azar is a fatal disease, Oriental

sore is eminently benign. It is known that one attack of Oriental sore confers immunity against further attacks of the same disease. Oriental sore is a disease of camel-using countries. It is said to affect dogs and possibly other animals. May it not be that the virulence of the Leishman body is removed by passage through the camel or some other animal; or, possibly, by being transmitted by some intermediary other than that which transmits the virulent kala-azar? If this be so, we have at hand a vaccine against kala-azar. This idea is worth testing: are those who have had Oriental sore immune as regards kala-azar, and *vice versâ?*"

So far, this important suggestion did not seem to have been taken seriously, and most authors had dismissed it by stating that it was negatived by the different geographical distribution of the two diseases.

Quite recently, Dr. Nicolle had suggested that the likewise indistinguishable parasite found in the spleen and other organs of children suffering from splenic anæmia in Tunisia should be looked upon also as a distinct species, and called *Leishmania infantum;* and Dr. Darling had advanced that the same parasite found in two negroes from Martinique and a Chinaman from Canton—all of whom had resided for a longer or shorter period in the Panama Canal zone—should be considered not only as belonging to a distinct species, but to an entirely new genus, and proposed calling it *Histioplasma capsulatum.*

He did not think they could accept Nicolle's and Darling's suggestions. Nicolle did not give any reason why they should look upon the parasite found in Tunisian children as distinct from that found in the children and adults of other countries, and the morphological differences indicated by Darling, as distinguishing his parasite from that of typical kala-azar, were the very characters

which, according to Statham, distinguished the kala-azar parasite taken from the cadaver some time after death, when probably the lowered temperature and the altere conditions in the tissues had promoted the first stages of a development ordinarily undergone in the gut of the invertebrate host.

Dr. Sambon considered that the present tendency to split up diseases and parasites into multitudinous types was in many instances erroneous, and could only lead to greater confusion in a matter already exceedingly complex. He made that statement all the more readily because he had himself followed such lines. Indeed, at the 1905 meeting of the British Medical Association, he had suggested that probably in relapsing fever, owing to its wide geographical distribution and to the different kinds of arthropoda concerned in its transmission in the various zoo-geographical regions, they might be able to distinguish various types of the disease due to different varieties or sub-species of *Spiroshaudinnia recurrentis*, and now, to his surprise, he found Professor Nuttall and other authorities on protozoa enumerating no less than five different species supposed to give rise to as many separate forms of relapsing fever! He believed these species to be founded on very doubtful characters, and even doubted whether the majority of them could be looked upon as separate varieties. Recent observations which he had been able to make whilst studying certain epizootics (diphtheria, pneumonia, tuberculosis, and various other diseases of protozoal or metazoan causation), affecting many different kinds of animals, had convinced him that whilst undoubtedly they would have to add new diseases to those already known, many others, now looked upon as distinct entities, would have to be reunited.

With regard to Leishmaniasis, he would not only include under the same term the epidemic kala-azar of Assam, the infantile splenic form described by Nicolle from Tunisia, the lung form seen by Darling in Panama, and the cirrhotic liver form of Rogers, but also the cutaneous form of a hundred names now generally called "Oriental sore."

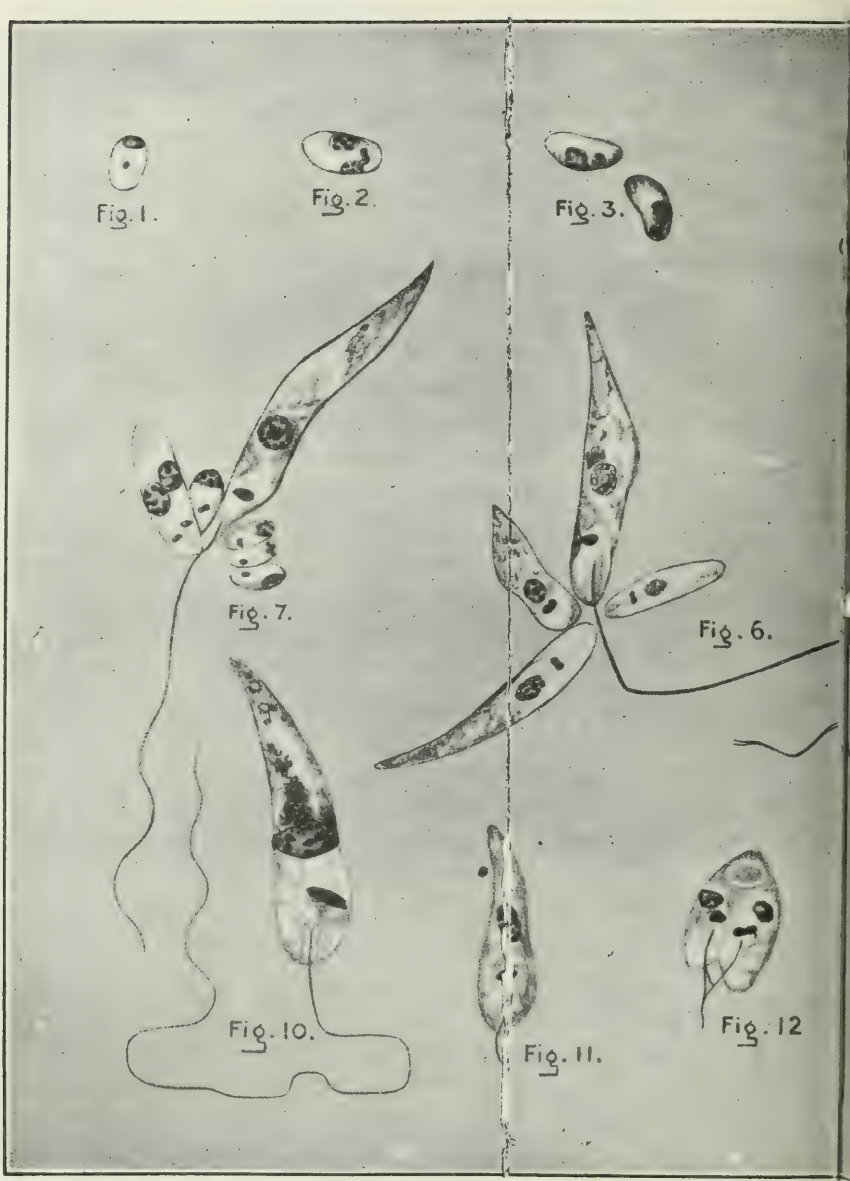
It would not be the first time in the history of medicine that the discovery of the specific agent enabled them to ascribe to a common cause unlike morbid manifestations previously looked upon as entirely distinct diseases. He need but mention tuberculosis and syphilis.

Concerning the identity of Oriental sore and kala-azar, he had already said that it had been opposed on account of difference in geographical distribution. So far as he could judge from the available data, the facts of geographical distribution were decidedly in favour of a relationship between the two forms of disease; but, to thoroughly understand the geographical data, it was necessary to master the complex œcology of the disease, and especially the different local causes which determined the prevalence of one or other form of the distemper.

He wished above all to discuss the striking difference between the local benign form called "Oriental sore" and the deadly general form called kala-azar, to endeavour to show that it was by no means opposed to a common cause, but, on the contrary, greatly in favour of it. There were many analogous examples to illustrate the relationship and explain it in the most satisfactory manner.

They might take tuberculosis as an example. The multitudinous forms in which that infection might manifest itself were well known. How different were the local cutaneous manifestations from the general infection! They all knew perfectly well that when transmitted by

PLATE II.—Herpetomonas Lyga



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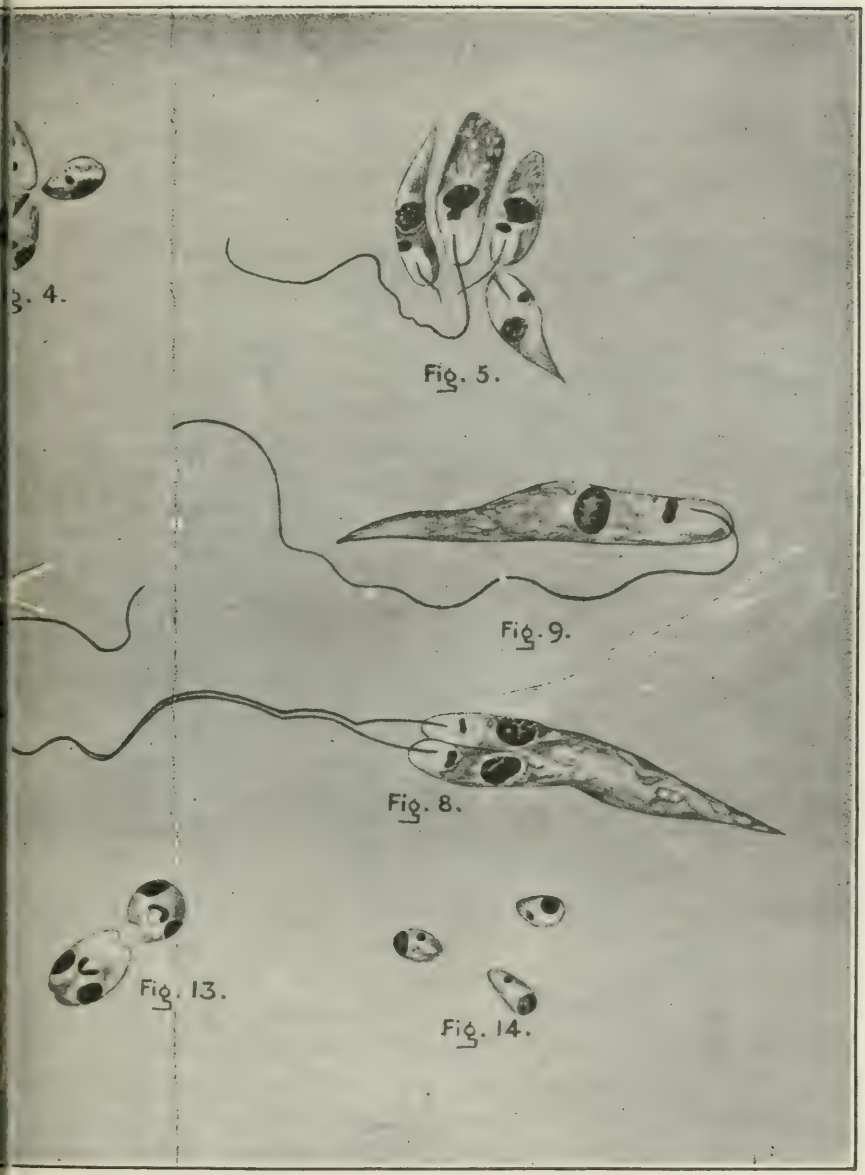

inoculation into the skin, as might occur amongst demonstrators of anatomy, butchers, and handlers of hides, one got a strictly local manifestation, in the form of a reddened mass of granulation tissue usually capping the dorsal surfaces of the hands or fingers, the so-called *post-mortem* wart, or the *verruca norvegica* of Wilks. That lesion so closely resembled Oriental sore that the latter had indeed been taken for a form of cutaneous tuberculosis, and Lewis and Cunningham had even proposed to call it *lupus endemicus*.

In anthrax they had another suitable example. There also the so-called "external anthrax" or "malignant pustule" might remain localized and curable. The regions of the body most frequently attacked were, as in Oriental sore, the face, neck, and hands.

But perhaps the best example was that of vaccinia, a local manifestation of variola, usually conveyed to cattle during the milking process by farm hands previously employed in dressing horses suffering from "grease" or horse-pox. Local manifestations of small-pox could be reproduced in man by smearing the abraded skin with matter from pustules of either vaccinia, horse-pox, sheep-pox, or human variola, and the practice was almost as old as the history of mankind. The Chinese practised variolization at least 3,000 years ago, and vaccination was known and practised in England, Germany, and other countries long before Jenner advocated its general use as a prophylactic against the deadly general infection.

Just as small-pox was inoculated in order to obtain a local and mild manifestation of the disease that might confer protection against the far more dangerous general infection, so, from time immemorial, in certain places, had Oriental sore been intentionally transmitted by inoculation to guard against more fearful consequences.

How could they explain the local limitation of cutaneous inoculations in diseases such as variola, anthrax, tuberculosis and kala-azar? It had been suggested that the absence of tendency to generalization might be due to the special structure of the skin or to its lower temperature, and experiments had proved that adipose tissue and dense connective tissue were unfavourable to the propagation of pathogenic organisms. To these reasons others might be added. Thus it was quite likely that, in the case of pathogenic agents which had a wide zoological distribution, a different zoological source might account for differences in virulence and location. That belief was founded not only on the observation of natural facts, but also on the result of experimental investigation. Bacteriologists were constantly either exalting or attenuating the virulence of disease-producing microbes by successive passages through the organisms of different animals, and they had noticed again and again that microbes obtained from a diseased organ, when introduced into other animals, usually localized themselves in that part which had been attacked in the first subject.

In the case of Leishmaniasis, they knew that the infection had been noticed in horses and dogs. In the dog, the cutaneous form had been early recognized in India, Persia, and Syria; it presented itself almost invariably on the bare tip of the nose. The general infection had been demonstrated only quite recently by Nicolle in Tunisian dogs. Nicolle had not only found the "Leishman-Donovan bodies" in the spleen and bone-marrow of stray local dogs, but had succeeded in reproducing the infection in other dogs by means of the inoculation of infected splenic blood into the liver and peritoneal cavity of normal puppies. Nicolle's experiments presented the objection of being carried out in a place in which dogs

were naturally infected; but, quite recently, Novy had been able to reproduce the infection in dogs in Michigan, U.S.A., where the disease was unknown, and the parasites he had inoculated were not of canine but of human source, obtained indirectly from Nicolle.

Besides the horse and dog, other animals, both wild and domestic, were probably concerned in the spread and conservancy of kala-azar, and he would point out more especially certain ruminants such as camels, oxen, and sheep. A vague relationship between camels and Oriental sore had already been suggested by Dr. Crombie, and parasites similar to the "Leishman-Donovan bodies," whether pertaining to Surra infection or not, had been seen by Lingard and others in these animals. In sheep, the presence of "Leishman-Donovan bodies" was very clearly indicated, he thought, by the presence of exactly similar bodies as well as flagellated forms in the mid-gut of *Melophagus ovinus*, a wingless, parasitic fly of the family *Hippoboscidæ*, strictly limited to sheep. The finding of similar parasites in a large number of insects belonging to the most sundered groups showed that that kind of organism must also have a wide range of vertebrate hosts, and their possible relationship to already known forms of animal trypanosomiases should not be overlooked.

Another fact to which he was inclined to give much importance was the particular stage reached by the parasite at the time of its transmission from one host to another. Christophers and others had shown that, towards the end of the kala-azar infection, ulcerations usually appeared on the skin and on the intestinal mucosa. The parasites found in these ulcerations were, he would suggest, obviously the forms of a spent infection which needed sexual rejuvenation. Inoculated

directly into the skin of a fresh host they would probably multiply more readily and give rise to much local reaction, but they would not tend to invade the organism of the host; their tendency must be to travel to the exterior for the purpose of being taken up by an appropriate host, in the body of which they might accomplish their sporogony. Thus it might well be that the general infection could only arise from the inoculation of young forms (sporozoits) by such insects as might subserve them as definitive hosts, whilst the localized cutaneous form might be the result of the direct inoculation of adult forms (sporonts) conveyed in a mechanical way either by insects or contaminated objects. Certainly asexual multiplication could not continue indefinitely, especially in the same host, and they knew perfectly well that in all animals presenting asexual multiplication a sexual act, or some other form of rejuvenation, was necessary from time to time for the continuance of the species. He believed, therefore, that it was not unreasonable to surmise with Manson that kala-azar might be a general infection caused by the "Leishman parasite" and conveyed from man to man, or from certain animals to man, by the agency of the rounded bed-bug or of some other insect capable of subserving its sporogony, and Oriental sore a localized cutaneous manifestation, due to the same parasite, conveyed from man to man, or from certain animals to man, through the agency of the common house-fly or some other insect which might or might not be necessarily concerned in its development.

The question was one of the highest importance with regard to the prophylaxis of this deadly and widespread scourge of tropical and sub-tropical countries, and considering how easily it could be done, it was surprising that no one had attempted hitherto to prove or disprove the hypothesis.

Dr. Low, after thanking Captain Patton for his interesting paper, said he would like to ask him a question on the development of the forms illustrated on the blackboard. He could not himself say that it was definitely certain yet that the Leishman parasite was a herpetomonas, though it had, as the lecturer had pointed out, many resemblances, especially in the flagellate form. It did not appear that these forms of herpetomonas represented went through any sexual development, but simply reproduced by fission in the body of the fly. On the other hand, the Leishman body was a cellular parasite and apparently to go through its development must have an extracorporeal sexual life-cycle in the bug. He thought there was enough evidence (apart from resemblances) to differentiate it into a different parasite altogether. One must be careful with regard to resemblances. In trypanosomes he had seen forms which were really very difficult to distinguish from the young forms of Leishman-Donovan bodies, and therefore he thought superficial resemblance between the first stages of parasites should not be allowed too much weight. He (Dr. Low) was certain that the parasite of Oriental sore was different from that of kala-azar. He had recently seen two cases of Oriental sore from Persia. He had asked one of them whether kala-azar existed there, and the answer was most emphatically, that it did not, or at least was very rare.

He did not know anything about the new parasite of infantile splenomegaly ; he had seen the one of Darling, and he was inclined to think it distinctly a different parasite from the Leishman-Donovan body.

As regards the life-history of the parasite in the bug, he found it very interesting, but it would be of great advantage if one could prove transference back from the bug. Experiments on dogs had always failed, but if we

could get some different animal that was susceptible we could then define the exact life-cycle of the parasite. The bug might after all not be a true intermediate host, though at present everything pointed to the fact that it was.

Sir HAVELOCK CHARLES, after congratulating Captain Patton on the able and lucid manner in which he had brought the subject before them, said there was one point on which he desired to gain a little light. The question was, the relationship between Oriental sore and kala-azar. Dr. Sambon had taken practically as proven that a close relationship existed. He (Sir H. Charles) had had considerable experience on the North-west frontier of India, in Persia, Turkestan and Beluchistan. He had lived amongst camel-drivers in a camp of 2,000 to 3,000 camels. He had treated natives for Oriental sore and also Europeans, and had seen a great deal of it. He had also seen it on the North-west frontier of India. Throughout the whole of the time he had been in these districts, and for twelve years in the Punjab, he had never seen one case of kala-azar. Subsequently, in Lower Bengal he saw plenty of it. On the frontier of India camels were in abundance; in Rajputana and in the Punjab they were very numerous; yet kala-azar did not exist there. In Lower Bengal (which is not a country for the camel, for it cannot live there) kala-azar was abundant. This state of things, he thought, obtained in Madras. Now, as Dr. Low pertinently pointed out, if there were a relationship between the parasites—if the one disease were the cause of the other—then wherever Oriental sore existed there we should also find kala-azar.

Dr. WENYON said there were one or two points in connection with these flagellates which were of interest

He thought they should not draw so hard and fast a line between forms which were herpetomonas and forms which were trypanosomes. It was very likely that herpetomonas was the primitive form of flagellate which, in biting flies, had gained entrance to the bodies of vertebrates and had there become a trypanosome. In the majority of the trypanosomes of vertebrates there was no herpetomonas stage known in the vertebrate host. By herpetomonas forms he meant those in which the nucleus and micro-nucleus were arranged in the opposite way to which they were in the ordinary trypanosomes. There were stages in many forms of trypanosomes which closely resembled herpetomonas. The *Trypanosoma theileria* parasite of South African cattle was an example; both forms were also to be seen in the case of a trypanosome of a snake recently discovered by him. A German investigator had lately described a trypanosome which showed both herpetomonas and trypanosome forms. The French Commission, which was investigating trypanosomiasis at the present time, had given a description of the development of trypanosomes in the proboscides of *Glossina palpalis;* the trypanosomes in this case developed into typical herpetomonas forms which remained attached to the inner surface of the proboscis. This fact, and other facts similar to it, had been brought forward in support of the contention that trypanosomes might develop into herpetomonas. It was a curious thing that the influence of the blood of the vertebrate host on herpetomonas seemed to produce the trypanosome type, while the reverse was also true that when the trypanosome left the vertebrate host it tended to revert to the herpetomonas type. The cultivation of trypanosomes in test-tubes gave rise to herpetomonas forms, and it was probable that trypanosomes in the intestines of insects gave rise to herpeto-

monas forms there also. In connection with the parasites of kala-azar, Captain Patton's study of the herpetomonas forms was useful in throwing light on these parasites. He (Dr. Wenyon) had seen herpetomonas-like forms in the melophagus of the sheep, and several other insects. There one frequently found these forms hanging on to the epithelium of the gut, but the cycle did not necessarily pass directly on from round forms to flagellate and then back to round forms again as indicated by Captain Patton. Possibly, when the nutriment in the intestinal tract becomes deficient, then the herpetomonas attach themselves to the gut and become what is called a "resting" form. When fresh nutriment passes into the gut the herpetomonas detach themselves and again become free swimming flagellate forms.

Sir PATRICK MANSON said it was very evident that the subject was an exceedingly complicated one. It was very dangerous for anybody to assume that the life-history of the Leishman body was even approximately known. One thing that had struck him in looking at the figures given by Captain Patton was that they differed considerably from the figures given by Colonel Leishman (and, he rather thought, by Captain L. Rogers) representing the development of the Leishman body in artificial cultures. If he recollected aright, Leishman represented the development of the dividing flagellate form in culture in this way: nucleus divided, blepharoplast divided, but the flagellum did not divide, the young flagellum being developed from the body protoplasm. Now, if this were the case, it was just possible that Captain Patton was dealing, not with a Leishman body, but with some other parasite. Another criticism he (Sir P. Manson) would offer —and Captain Patton must bear in mind that though he

criticized he did not condemn—Captain Patton had, for example, in describing *H. muscæ domesticæ* assumed that the fly was infected by feeding on the excreta of another fly. He questioned very much the probability of this; it was an assumption which required to be proved before being accepted. Another point he would refer to was the identity, or non-identity, of the parasites of kala-azar, infantile splenomegaly and Oriental sore. Either was quite possible, but neither had been proved. Sir Havelock Charles said he had not met with kala-azar in the regions where Oriental sore was prevalent, and *vice versâ*, and from that fact he drew the conclusion that the diseases could not be identical. Dr. Sambon opposed this objection very aptly by saying that people living in the regions of Oriental sore were all vaccinated against kala-azar, and those living in the regions of kala-azar were vaccinated against Oriental sore. It was a very odd thing that the disease of infantile splenomegaly was a very serious disease as regards man and a non-fatal disease in the lower animals. Novy obtained parasites of infantile splenomegaly and inoculated several hundreds of cultures of this parasite into a dog, and failed, as he thought, to produce an infection. There was no clinical evidence whatever of successful infection. After many months he killed the dog and was surprised, on examining smears taken from the liver, spleen, and bone-marrow, to find them crowded with Leishman-Donovan bodies; thereby showing that this parasite, which was fatal in man, was harmless in dogs. He (Sir P. Manson) thought it was a justifiable speculation that something similar might occur in the case of the kala-azar parasite in its relationship to Oriental sore. The subject was well worth further investigation. From a practical point of view the parasite of Oriental sore afforded a splendid

opportunity for working out the life-history of the kala-azar parasite. No one was justified in experimenting with so deadly a parasite as that of kala-azar, but one was justified in experimenting with the parasite of Oriental sore; if experiments with the latter were successful they might throw light on kala-azar. Vigorous efforts should, therefore, be made to work out the life-history of the parasites of Oriental sore.

Captain PATTON, in reply, said that, owing to the shortness of his paper, he had been unable to deal with all the points which had been raised in the discussion; he wished, however, to correct some erroneous views. Dr. Sambon had spoken in a very loose way of the sexual forms of these flagellates of insects, but he (Captain Patton) would like to point out that there was not the slightest evidence at present to support the view that they had such stages; the so-called male, female, and indifferent forms merely representing parasites of varying ages which had resulted from equal or unequal longitudinal division of adult parasites. The thin forms which Leishman had described splitting off from the adult flagellates of the parasite of kala-azar were certainly not sexual forms; a large number of these flagellates exhibited this marked polymorphism, and the conjugating forms of some writers were readily explained by the unequal longitudinal division of the adult flagellate.

In going into the history of these so-called developmental forms of vertebrate trypanosomes in invertebrate hosts, it is quite evident that natural flagellates of the invertebrate hosts have been entirely omitted; he (Captain Patton) said that in a paper shortly coming out in the *Journal of Parasitology* (vol. i., part iv.), he had written a critical review of the whole subject, and would

refer Drs. Sambon and Wenyon to that paper. He would, however, make some comments on one of the so-called developmental stages of a vertebrate trypanosome. It will be remembered that Prowazek described the life-cycle of *Trypanosoma lewisi* in the louse (*Hæmatopinus spinulosus*), and according to his observations it passes through a complicated sexual cycle in the louse, so that this insect ought to be the true host of the trypanosome. No other observers, however, have been able to find these stages, and he (Captain Patton) had also searched for their developmental forms without success; recently, in Cambridge, he had had the opportunity of studying a flagellate of the rat-flea (*Ctenophthalmus agyrtes*), which was not unlike Prowazek's developmental forms in the rat-louse. He knew, however, that this flagellate was a true parasite of the rat-flea and belonged to the genus *Crithidia*. *Herpetomonas* and *Crithidia* were very like each other in their immature stages, and if this stage alone were studied it was impossible to differentiate between them. In their adult flagellate stages they were, however, quite distinct, and the occurrence of *Crithidia* in blood-sucking insects has led numerous observers to describe them as developmental forms of vertebrate trypanosomes; in certain stages of their development some of these flagellates were like small trypanosomes. He (Captain Patton) had not touched upon the hereditary transmission of these flagellates, but he was well aware that the flagellate of the sheep-bred *Melophagus ovinus* was a crithidia, and that it was transmitted hereditarily; the complete life-cycle of this parasite would shortly be described by Swingle, who would prove that it had no connection with any blood parasite of the sheep.

With regard to Dr. Sambon's remarks as to Oriental

sore occurring in camel-using countries, he (Captain Patton) had had a good deal of experience with Arab camel-drivers who frequently suffered from similar sores on their legs and sometimes on their faces. By Oriental sore he meant a sore in which the characteristic parasite (*H. tropica*) had been found. Arabs of the Aden Hinterland often developed these sores after the bites of *Ornithodorus savignyi*, and he had examined a large number of scrapings from these sores, but had never been able to find any parasites. He contended that the sores occurring in camel-using countries were not necessarily true Oriental sores, and that that term was used far too loosely. His observations were quite in agreement with those of Sir Havelock Charles, that kala-azar and Oriental sore were two distinct diseases.

Dr. Wenyon had drawn attention to the difficulty of drawing a hard and fast line between herpetomonas and trypanosome. He (Captain Patton) was well aware that trypanosomes when cultivated in test-tubes showed multiplication forms not unlike young herpetomonads; from this he thought it was only possible to say that trypanosomes had at some time or other evolved from herpetomonads. It should, however, be noted that it had not yet been proved that the well-known vertebrate trypanosomes pass through multiplication stages similar to herpetomonas and crithidia in the intestinal tract of blood-sucking invertebrates. A true herpetomonas or a crithidia, however, never became a typical trypanosome. With regard to the flagellates of leeches, he had found that a leech common on frogs in Madras had a crithidia of its own which was in no way connected with the frog trypanosomes ingested by the leech.

Sir Patrick Manson had criticized his observations on the development of *H. donovani* in the bed-bug (*Cimex*

rotundatus), suggesting that it may be a true parasite of the bug and have no connection with the human parasite. This criticism was quite justifiable, and he (Captain Patton) had paid special attention to this possibility. When carrying out his feeding experiments in Madras, he obtained a collection of bugs from almost every large town in India, as well as from Mauritius, North and South Africa, and China; the majority of the insects were alive when they arrived. He had dissected a large number of these bugs in order to find out whether they had a natural parasite of their own, but he was unable to find any. He had recently inoculated dogs with *H. donovani* in the same way as Nicolle; after keeping the dogs for two months they were killed, and on examining their organs he was unable to find a single kala-azar parasite. So far as he was able to ascertain, dogs in Madras did not harbour this parasite.

"JEDDA ULCER" AND THE NON-IDENTITY OF NILE BOILS WITH ORIENTAL SORE.

By F. M. SANDWITH, M.D., F.R.C.P.

This specimen from the skin of an adult Arab of Jedda was kindly sent to me by Dr. J. E. Creswell, of Suez, labelled "Jedda Ulcer," and I do not know that I am justified in rechristening it, though I should be unwilling to add to the long list of names by which the disease is already known. Its official name is "Oriental Sore," but I am interested to see that the latest French author of a tropical book has called it *Leishmaniose cutanée* (Neveu-Lemaire, 1908).

The etiology of Oriental sore is still obscure, though most writers incline to the belief that the parasite is probably inoculated by means of a biting insect.

Our earliest accounts date from Aleppo in the middle of the eighteenth century. Volney says that the inhabitants of Aleppo were mostly disfigured by scars on the face, and he accepts the native belief that the malady was due to bad drinking water. This supposed cause was repeated by various writers for more than 100 years, and is still believed in by many Orientals. It is also stated that in India and elsewhere the disease has become less prevalent since the improvement of the water supply. As the disease is confined to tropical and sub-tropical climates, is observed more frequently in towns than in country districts, is usually present on uncovered parts of the body, and can be communicated by inoculation

to a healthy person, it is quite possible that the parasite is conveyed to man by some water-loving and town-dwelling insect, living, for instance, in cisterns. The seasonal influence is also in favour of this theory, for the disease is most common in the autumn months, when gnats and other insects, which thrive in moderate heat, are most numerous in towns, and the season often corresponds with the date harvest, and has therefore been supposed to be connected with it (like dengue). In Tashkend the disease has been called for years the "fly bite." It would be interesting to know whether Oriental sore is ever met with in residents above the mosquito zone, say, 6,000 feet above sea-level. Another interesting point is the reported immunity of children during their first year of life, which, if true, must be difficult to explain by those who believe that the disease is contracted during the act of washing.

All books which refer to the geographical distribution of Oriental sore include Egypt as one of the countries in which it is endemic. Judging by the experience of the last twenty-five years, this is not strictly accurate, for all the Egyptian cases of which I know have been imported into Egypt from neighbouring countries. The evidence in favour of its having existed in Egypt in former days is mostly taken from Pruner's book, who, writing in 1846 from Cairo, says that he saw *bouton d'Alep* there in men who had not been in Syria for forty years, and also that he saw it in Cairo in English officers from Sindh in India. He further states that in his twelve years' hospital experience in Egypt he often saw the "Yemen ulcer" cured in Cairo; this would probably be among Egyptian troops returning from the campaigns in Syria, but it might to-day be called tropical phagedæna.

It is quite true that the well-known Nile boil, some-

times called by French writers *bouton du Caire*, has some points of resemblance with Oriental sore, for it attacks newly-arrived residents during their first or second season of damp heat, and it sometimes seems to confer immunity from future trouble of this kind. It is followed by unsightly scars, and the boil can be reproduced in a healthy man by inoculation, for Professor Chantemesse[1] performed this experiment in Paris with matter taken from a boil which had been sent to him intact from Cairo.

Unlike Oriental sore, the distribution of the Nile boil is not confined to uncovered parts. It prefers the situations ordinarily selected by boils, chiefly those where there has been some slight irritation of the skin; it does not usually proceed to ulceration, and it does not last for several months, like the Oriental sore, for no individual boil usually remains more than fourteen days. Moreover, Professor Symmers made a culture on the third day from one of Mr. Madden's cases in Cairo and "grew a pure culture of *Staphylococcus pyogenes aureus*."[2]

I venture to suggest that it is unwise to continue in the belief that Egypt is the seat of Oriental sore, until the disease is discovered there in a person who has not left that country during the preceding two years, and who has not been directly inoculated from an imported case.

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[1] *Annales de l'Inst. Pasteur*, 1887, p. 477, or *Bull. de la Soc. Anat.*, 1887, p. 576.

[2] "Nile Boils," by F. C. Madden, *Journal of Tropical Medicine*, 1906, p. 294.

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